CLINICAL ARTICLE

A logistic model for the prediction of endometriosis

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Objective: To develop a model that uses individual and lesion characteristics to help surgeons choose lesions that have a high probability of containing histologically confirmed endometriosis.
Design: Secondary analysis of prospectively collected information.
Setting: Government research hospital in the United States.
Patient(s): Healthy women 18–45 years of age, with chronic pelvic pain and possible endometriosis, who were enrolled in a clinical trial.
Intervention(s): All participants underwent laparoscopy, and information was collected on all visible lesions. Lesion data were randomly allocated to a training and test data set.
Main Outcome Measure(s): Predictive logistic regression, with the outcome of interest being histologic diagnosis of endometriosis.
Result(s): After validation, the model was applied to the complete data set, with a sensitivity of 88.4% and specificity of 24.6%. The positive predictive value was 69.2%, and the negative predictive value was 53.3%, equating to correct classification of a lesion of 66.5%. Mixed color; larger width; and location in the ovarian fossa, colon, or appendix were most strongly associated with the presence of endometriosis.
Conclusion(s): This model identified characteristics that indicate high and low probabilities of biopsy-proven endometriosis. It is useful as a guide in choosing appropriate lesions for biopsy, but the improvement using the model is not great enough to replace histologic confirmation of endometriosis. (Fertil Steril® 2008;■:■–■. ©2008 by American Society for Reproductive Medicine.)

Key Words: Endometriosis, prediction, logistic regression modeling

According to the 2005 European Society of Human Reproduction and Embryology guidelines (1), the 2000 American College of Obstetricians and Gynecologists Practice Bulletin (2), and the 2005 American College of Obstetricians and Gynecologists Committee Opinion (3), in some circumstances, it is acceptable to diagnose endometriosis on the basis of the visual appearance of lesions at laparoscopy. In questionable cases, biopsy with histologic confirmation of the disease is recommended, but positive histology is not a requisite for diagnosis in all cases. The responsibility of identifying endometriosis rests with the surgeon, who must recognize endometriosis by using only visual assessment at surgery (4).

Unfortunately, visual assessment of lesions has poor intraphysician agreement and high rates of misdiagnosis (5) and correlates poorly with actual histologic findings (4, 6–14). Presurgical screening tests to increase the probability of a woman having endometriosis at surgery are one way to improve the likelihood of accurate diagnosis. However, questionnaires, magnetic resonance imaging, ultrasound, and adjunctive lab tests all lack the sensitivity and specificity to significantly increase the pretest probability of disease (1, 8, 11, 15, 16), except in the case of women with severe endometriosis (stages III or IV) (6, 17–19). On the basis of these facts, some method is needed to assess which lesions are most likely to represent true disease, particularly if visual appearance is used.

At surgery, endometriosis lesions present with a variety of colors, sizes, and locations (8, 10, 11, 15, 20). The heterogeneity of lesion characteristics suggests that visual inspection

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may not be sufficient to identify endometriosis (9), especially when subtle lesions are present. Thus, development of a model synthesizing multiple factors may improve the accuracy of diagnosis or at least guide the surgeon regarding which lesions are most likely to be positive on biopsy. By correlating patient and individual lesion characteristics with pathologic findings in a multivariate regression model, we sought to assess which lesions are most likely to be biopsy confirmed as endometriosis. This understanding may allow improvement on the poor correlation of histology with surgical assessment (4, 6–14).

MATERIALS AND METHODS

This is a secondary data analysis of a clinical study that received institutional review board approval from both the National Institutes of Health and the University of North Carolina at Chapel Hill. Data were collected from 119 women who were 18–45 years of age and who were enrolled in a clinical trial for the treatment of chronic pelvic pain and endometriosis from 1999 to 2004 that combined laparoscopic excision of all lesions with medical treatment. Women were healthy, with the exception of pelvic pain lasting ≥ 3 months.

Data Collection

After providing informed consent, all participants underwent laparoscopy. At surgery, information was collected on all visible lesions, as described elsewhere (11). Lesions suspected of being endometriosis were excised with contact neodymium: yttrium-aluminum-garnet laser (Surgical Laser Technologies, The Oaks, PA); no lesions were ablated, and all were sent for histology. When cysts were present, the walls were stripped from the surrounding tissue. An appendectomy was performed if there was chronic inflammation or endometriosis involving this structure. Peritoneal defects were excised in toto whenever possible. To minimize unreasonable risks to the patient, deep implants were not resected if they were found in the rectovaginal septum or transmural to the bowel wall.

The following categories were used to identify the location of the lesion: bladder peritoneum, round or broad ligament, colon or appendix, cul-de-sac, ovarian fossa, ovary, sidewall, uterosacral ligament, and uterus or fallopian tube. Each lesion was measured across two diameters, which were averaged. If lesions were closely spaced (within 0.5 cm of each other), the measurement included the distance across all lesions. Color categories included red, white, black, mixed, and endometriomas, and the type of lesions (endometriotic vs. nonendometriotic), as judged by the surgeon, also was recorded. Finally, the revised American Fertility Society classification system was used to estimate the severity or stage of the disease in the pelvis (21).

Histology was considered to be positive only if both endometrial glands and stroma were identified.

All lesions that were identified as endometriosis by the surgeon were eligible for inclusion in the model. To remain in the data set, the observation for each lesion had to have complete covariate data of lesion characteristics, as well as histology results, revised American Fertility Society disease stage, and patient demographics.

Data Analysis

For the model development, data were randomly allocated to one of two data sets (designated the *training* and *test* data sets) by using STATA (version 8.2; STATA Corporation, College Station, TX). The model was developed in the training data set and validated in the test data set. Univariate analysis was performed for each variable to assess distribution and the need for transformation.

The model was developed by using logistic regression with the histologic diagnosis of endometriosis as the outcome of interest. Variance estimates for individual parameters were adjusted for multiple observations taken from single participants and for the nonindependence of these observations. Lesion color, location, stage, and race were treated as categorical variables. Age, body mass index (BMI), and lesion width were evaluated for linearity in the logit before being included as continuous variables. Transformations were not required for these variables. Categorical variables were condensed on the basis of similarities of the estimates in the model and tests of heterogeneity across categories. Therefore, categories were constructed on the basis of mathematical, not clinical, criteria.

The Hosmer-Lemeshow goodness-of-fit test was used to test the predictive ability (calibration) of the model. The area under the receiver operating characteristic curve was used to evaluate the discrimination of the model fit. Sensitivity, specificity, positive predictive value, and negative predictive value, as well as percentage of lesions correctly classified, were calculated for the combined data. Analyses were performed by using STATA, version 8.2.

RESULTS

There were a total of 530 observations from 119 women that potentially were eligible for inclusion in the model. Forty-three observations (8.1% of the complete data set) were dropped during modeling because of missing covariate information. There were a total of 114 women contributing complete data on 487 lesions; of those lesions, 320 (65.7%) had histologically confirmed endometriosis. Approximately two thirds of the observations ($n = 334$) were included in the training data set, and the remainder ($n = 153$) were included in the test data set. Because each lesion was considered separately during the allocation process, the same woman could contribute lesions to both data sets. Thus, 104 women contributed to the training data set, and 77 women contributed to the validation data set.

Of women in the complete data set, 92 reported their race as white (80.7%). Forty (35%) had stage I disease, 46 (40%) had stage II disease, 17 (6%) had stage III disease, and 11

TABLE 1

Distribution of lesion characteristics, odds ratios for association of lesion characteristics with histologically confirmed endometriosis, and calculated probability of histologically confirmed endometriosis of each characteristic (derived from the model after adjustment of all other variables).

Lesion characteristics	n (%)	Odds ratio (95% confidence interval)	Adjusted probability of endo+ (95% confidence interval)	% Change from referent
Location[a]				
Bladder peritoneum, round or broad ligament, sidewall	129 (26.5)	0.42 (0.25, 0.71)	0.44 (0.15, 0.78)	−22
Uterus, ovary, fallopian tube	106 (21.8)	0.50 (0.26, 0.97)	0.49 (0.18, 0.81)	−17
Cul-de-sac, uterosacral ligaments (referent)	196 (40.3)	—	0.66 (0.30, 0.89)	—
Ovarian fossa, colon, appendix	56 (11.5)	1.18 (0.70, 1.98)	0.69 (0.34, 0.91)	3
Color groups[b]				
Red or white	251 (51.6)	—	0.66 (0.30, 0.89)	—
Blue, black, brown, endometrioma	136 (27.9)	1.21 (0.76, 1.93)	0.69 (0.33, 0.91)	3
Mixed colors	100 (20.5)	1.87 (1.05, 3.34)	0.78 (0.44, 0.94)	12
Race[c]				
Nonwhite	82 (16.8)	0.67 (0.40, 1.12)	0.56 (0.22, 0.85)	10
White (referent)	405 (83.2)	—	0.66 (0.30, 0.89)	—
Stage[d]				
I	99 (20.3)	0.49 (0.31, 0.79)	0.48 (0.17, 0.81)	−18
II, III, IV	388 (79.7)	—	0.66 (0.30, 0.89)	—

	Median (range)	Odds ratio per unit increase (95% confidence interval)		
Width of lesion (mm)[d]	5 (1–90)	1.05 (1.02, 1.09)		
2.7			0.59 (0.25, 0.87)	−7
7.7 (mean, referent)			0.66 (0.30, 0.89)	—
12.7			0.71 (0.35, 0.92)	4
17.7			0.76 (0.40, 0.94)	8
22.7			0.80 (0.45, 0.95)	10
BMI (kg/m^2)[e]	24.3 (17.2–4.5)	0.97 (0.93, 1.01)		
35			0.59 (0.19, 0.90)	−4
30			0.62 (0.24, 0.90)	−2
25 (mean, referent)			0.66 (0.30, 0.89)	—
20			0.68 (0.36, 0.89)	2
15			0.71 (0.43, 0.89)	4
Age (y)[f]	31 (17–46)	1.01 (0.98, 1.04)		
21.4			0.63 (0.32, 0.87)	−2
26.4			0.64 (0.31, 0.88)	0
31.4 (mean, referent)			0.66 (0.30, 0.89)	—
36.4			0.66 (0.29, 0.91)	1
41.4			0.67 (0.28, 0.92)	2

Note: endo+ = endometriosis positive.

[a] For each calculation using location, color group = red or white (reference level); race = white (reference level); width = 7.7; stage = II, III, IV (reference level); BMI = 25 (reference level); and age = 31.4 (reference level).

[b] For each calculation using color group, location = cul-de-sac; uterosacral ligaments (referent); race = white (reference level); width = 7.7; stage = II, III, IV (reference level); BMI = 25 (reference level); and age = 31.4 (reference level).

[c] For each calculation using race, location = cul-de-sac; uterosacral ligaments (referent); color group = red or white (reference level); width = 7.7; stage = II, III, IV (reference level); BMI = 25 (reference level); and age = 31.4 (reference level).

[d] For each calculation using width, location = cul-de-sac; uterosacral ligaments (referent); color group = red or white (reference level); race = white (reference level); stage = II, III, IV (reference level); BMI = 25 (reference level); and age = 31.4 (reference level).

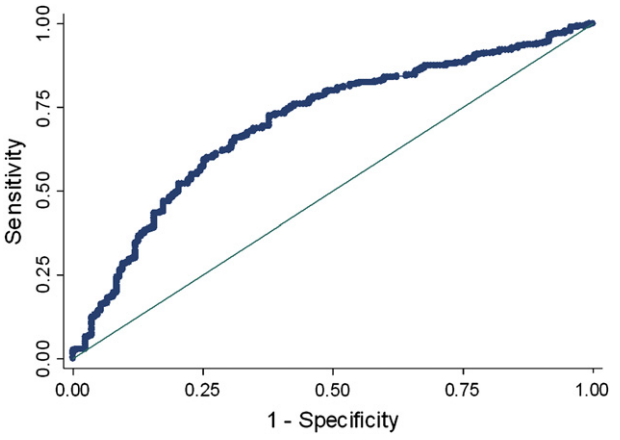
[e] For each calculation using stage, location = cul-de-sac, uterosacral ligaments (referent), color group = red or white (reference level), race = white (reference level), width = 7.7, BMI = 25 (reference level), and age = 31.4 (reference level).

[f] For each calculation using age, location = cul-de-sac; uterosacral ligaments (referent); color group = red or white (reference level); race = white (reference level); width = 7.7; stage = II, III, IV (reference level); and BMI = 25 (reference level).

Stegmann. Predictive model for endometriosis. Fertil Steril 2008.

FIGURE 1

Receiver operating characteristic curve. Model correctly predicts endometriosis 66.7% of the time. Area under receiver operating characteristic curve, 0.7026.



Stegmann. Predictive model for endometriosis. Fertil Steril 2008.

(9%) had stage IV disease. The mean age (± SD) of the study participants was 31.4 ± 7.2 years (range, 18–45 y), and their mean BMI was 25 ± 4.7 (range, 17.2–44.5). Forty percent of lesions were located in the cul-de-sac or uterosacral ligaments. The majority of the lesions were subtle lesions (red or white, 51.6%; Table 1). The distributions of age, race, BMI, stage, lesion location, color, width, and histologically confirmed endometriosis did not differ significantly between the training and validation data sets, suggesting that participant characteristics were reasonably well-balanced.

The Hosmer-Lemeshow goodness-of-fit test for the training data set was used to validate the model. The *P* value was estimated at .78, indicating good calibration of the model to the data set. The test data set had a *P* value of .30, again showing good calibration. The area under the receiver operating characteristic curve for the training data set was 0.70, indicating only fair discrimination of the model, which was similar to the case of the test data set, at 0.69.

After the model was validated, it was applied to the complete data set to determine characteristics that were predictive of endometriosis. Lesions located on the ovarian fossa, colon, or appendix were 25% more likely than were those on the uterus, ovary, fallopian tubes, cul-de-sac, or uterosacral ligaments to contain histologically confirmed endometriosis (Table 1). The odds that a given lesion was confirmed to be endometriosis increased by 5% per millimeter of lesion width (odds ratio, 1.05; 95% confidence interval: 1.02, 1.09). Lesions from women classified as having stage I disease were significantly less likely to contain endometriosis than were those from women with stage II–IV disease (odds ratio, 0.49; 95% confidence interval: 0.31, 0.79). The odds of lesions of mixed color truly containing endometriosis were 87% greater than those for lesions that were red or white (odds ratio, 1.87; 95% confidence interval: 1.05, 3.34), yet red or white lesions were as likely to be confirmed as endometriosis as were lesions that were blue, black, or brown or endometriomas. Age and BMI were not associated with changes in the odds of histologically confirmed endometriosis.

The model also was used to explore the change in the probability of confirming endometriosis by adjusting each variable in relation to the referent (most common) value for each characteristic. The largest change in percentage occurred among different locations (from –22% to +3%), and the smallest change was observed with age (from –2% to +2%). When the characteristics with the highest probability of confirming endometriosis were used, a nearly 3-cm-wide, mixed-color lesion in the ovarian fossa from a 42-year-old Caucasian woman with a BMI of 15 and at least stage II disease had the highest probability of endometriosis (92.9%; 95% confidence interval: 0.73, 0.98). By contrast, a small red lesion on the bladder peritoneum from a 22-year-old non-Caucasian woman with stage I endometriosis had the lowest probability of confirmed endometriosis (22.0%; 95% confidence interval: 0.09, 0.45).

We also determined the sensitivity, specificity, positive predictive value, and negative predictive value of the final model. The model predicted the presence of endometriosis with a sensitivity of 88.8% and predicted the absence of endometriosis with a specificity of 24.6%. The positive predictive value was 69.3%, and the negative predictive value was 53.3%. This equated to 66.5% correct classification of a lesion (Fig. 1).

DISCUSSION

Overall, this model had a modest ability to predict endometriosis from individual lesion characteristics. We found moderate associations between the characteristics of size, location, and mixed color with endometriosis, but as expected, no other single lesion characteristic predicted endometriosis with a high accuracy. Lesions of any single color had similar probabilities of being confirmed as endometriosis. A mixed-color lesion increased the probability of confirming endometriosis from 66% to 78%.

Lesion size and location were more helpful in predicting biopsy-positive endometriosis lesions. This model confirmed that wider lesions had a greater probability of containing endometriosis, with an increase of 17% noted in comparing a 2.7-mm lesion with a 27.7-mm one. Likewise, there was a 17% increase in the probability of confirming biopsy-proven endometriosis in identical lesions that were located in the ovarian fossa, compared with in the uterus. However, although endometriosis commonly was found in the cul-de-sac or on the uterosacral ligaments, location alone did not correlate well with the presence of endometriosis on biopsy.

This model provides guidance about appropriate lesions to biopsy for confirmation of the disease. Information about

subtle lesions may be useful in directing the surgeon to biopsy, atypical, low-probability lesions to ensure that endometriosis is the true diagnosis. For instance, a large lesion in the ovarian fossa that is of mixed color has a 93% probability of being endometriosis and may not need to be biopsied unless definitive diagnosis is needed, such as would be required for entry into a study protocol. However, a small red or white lesion on the uterus has just a 22% chance of containing endometriosis, and if other high-probability lesions are not seen, a biopsy of such a lesion would be appropriate to confirm the presence of the disease.

Overall, basing the diagnosis of endometriosis on subtle lesions alone is problematic because of the variable appearance of these lesions (4, 10–13). Martin et al. (4) reported a 30% increase in the diagnosis of endometriosis in women overall when biopsies were taken from all abnormal-appearing tissue (subtle findings) and not just from tissue suspected to be endometriosis. Until another method is found of easily identifying endometriosis in these lesions at surgery, our results indicate that it is prudent to use biopsy to confirm the diagnosis of endometriosis in women with atypical lesions.

Our model aptly described results in the study group but may not be generalizable to the population at large or to women who have infertility, but not pain. All subjects had symptoms consistent with pain associated with endometriosis; therefore, the findings at laparoscopy may be relevant for lesions likely to cause pain and not for infertility. Had we sampled women with pain-free endometriosis or those with infertility, we might have found different associations. However, random laparoscopies in asymptomatic women present ethical issues, and women with endometriosis-related infertility who are undergoing IVF may not undergo laparoscopy. Also, the clinical trial was not designed to define lesion characteristics, and normal peritoneum was not routinely sampled as a control. This may account for the low specificity and the low negative predictive value, because lesions believed to be negative were not routinely sampled.

In conclusion, our findings are consistent with those of reports published elsewhere (9), in that they indicate that use of lesion color is a poor predictor for the presence of endometriosis and that endometriosis is found with similar frequencies in lesions of any single color. Width, location, mixed color, and race were modestly predictive of endometriosis, whereas stage of disease was more strongly predictive. Overall, our model increased the sensitivity for identifying endometriosis in individual lesions from 65.7% to 88% but had poor specificity, meaning that we could not reliably predict lesions that did not contain endometriosis. This model was able to identify lesions with a high (93%) or low (22%) probability of containing endometriosis but also demonstrated the need for disease confirmation by biopsy in women with subtle lesions. The information that we have presented provides useful guidelines to aid in decision making about the likelihood of a patient having endometriosis at the time of surgery and to help differentiate between high- and low-probability lesions for biopsy if this diagnosis is in question, thus supporting excising rather than ablating any high-probability lesion. This model augments, but does not replace, clinical judgment.

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